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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,211	02/12/2004	Silvia Burvenich	1522-1003-1	4018

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EXAMINER	
THOMAS, DAVID C	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,211	BURVENICH ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2* is/are allowed.

6)☒ Claim(s) *1 and 3-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed November 29, 2006 is acknowledged. Claim 1 (currently amended) and claims 2-6 (previously presented) will be examined on the merits. Claims 7-32 were previously canceled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 and 3-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to methods for identifying a person at increased risk for developing Parkinson's disease, wherein the presence of a mutation causing truncation of the protein chain encoded by the ADH1C gene shows a significant association with Parkinson's disease in sample groups from a number of countries. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are drawn to identifying a person at increased risk for developing Parkinson's disease (but not any other diseases or clinical conditions) comprising screening nucleic acid samples from a patient and control subjects for a mutation in the ADH1C gene causing truncation of the expressed protein chain due to a stop codon. Samples are screened for such a mutation by any number of molecular analytical methods, including direct sequencing, restriction endonuclease cleavage, and oligonucleotide hybridization assays.

Quantity of Experimentation

The quantity of experimentation in this area is large since determination of the diagnostic efficacy of the method for identifying persons at increased risk for developing Parkinson's disease would require performance of this method on a large enough sample set to be statistically significant. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Major improvements in the technology would be required to demonstrate to what degree the invention can

identify cases of Parkinson's disease in patient samples, which would require large numbers of subjects and samples for performing both the necessary basic research and the follow-up clinical studies.

The unpredictability of the art and the state of the prior art

This is a very unpredictable art with regard to identifying a person at increased risk for developing Parkinson's disease, since many patients clearly do not display a nonsense mutation in the ADH1C gene. Though it appears that a nonsense mutation is found in samples from some Parkinson's disease patients but rarely in control samples (based on the Tables I and II in the specification), the fact that many patients do not possess such a mutation makes prediction of the disease impossible based solely on this type of genetic test, and limits the invention to identifying a person as being at increased risk for developing the disease or identifying a subset of persons who may already have the disease rather than identifying all persons with the disease.

Furthermore, the art indicates that not all ADH1C stop mutations are only found in PD patient samples. A small percentage were found in control samples (0.6%) compared to 2.0% of the PD samples (Buervenich et al. Arch. Neurol. (2005) 62: 74-78), though this difference was determined to be statistically significant. In a related study, Schmitt et al. performed an ADH1C stop mutation screening of samples from multiple system atrophy (MSA), a disorder with molecular similarities to Parkinson's disease, and found that 2.6% of MSA patients displayed the mutation in a British population sample set, compared to 0.43% in controls, a statistically significant difference (Mov. Disorders (2006) available online in advance of print, Sept. 7, 2006, pp. 1-2). However, in a German population sample set, while 2.1% of MSA patients were found to have a stop mutation, a relatively high 1.4% of the control samples had the

mutation, indicating that no significant association of the mutation with MSA was observed, and further suggesting that some populations may not be amenable to risk assessment for developing diseases such as PD or MSA based on presence of a stop mutation. Indeed, the German sample set measured by Buervenich indicated a relatively high 1.3% of control samples containing a stop mutation compared to 0.13% for other populations. Thus, even at present, there remains a high degree of unpredictability in the art with regard to the use of a molecular test such as an ADH1C stop mutation assay for identifying a person with a particular disease such as PD or predicting the risk levels for a person to develop the disease.

Similarly, earlier studies of alcohol dehyrogenase polymorphisms in another ADH gene revealed conflicting reports as to the relationship of such polymorphisms and Parkinson's disease. Using a Swedish population sample set, Buervenich et al. (Mov. Disorders (2000) 15: 813-818) reported an association of mutations in the ADH4 gene of PD patients compared to control samples. However, Tan et al. (Neuroscience Lett. (2001) 305: 70-72) found no correlation for mutations in this same gene for Hispanic and Caucasian sample sets compared to control samples, suggesting that differences may indeed exist between different populations, and that the predictability of PD by such tests may be more useful for some samples sets than others, but could also indicate the polymorphisms do not have any functional relevance to the etiology of the disease (Tan, p. 71, column 2, lines 14-22). The conflicting results may also indicate the difficulties in interpreting results from genetic studies of a multifactorial disease such as PD (Tan, p. 71, column 2, lines 6-14).

Working Examples

The specification has one working example, describing experimental methods to screen genomic DNA obtained from patients and control subjects for the ADH1C mutation. Table I indicates that no nonsense mutations (stop mutations) in the ADH1C gene are detected in control samples, while 1.2% of samples from Parkinson's disease patients have the specific mutation. Table II provides ADH1C stop mutation data from five international collection sites, again indicating that samples from Parkinson's disease patients, but not from control subjects, contain the nonsense mutation at a statistically significant frequency.

Guidance in the Specification.

The specification, while providing the experimental methods necessary to detect ADH1C stop mutations in patient samples, does not provide teachings sufficient to detect all stop mutations in the ADH1C gene in patient samples that may be indicative of an increased risk for developing Parkinson's disease. There is no indication that the technology is sensitive enough or that the sensitivity can be improved to detect all stop mutations in a sample set, but only to demonstrate that a small subset of the patients actually have a specific truncation mutation. Therefore, the invention is best suited as a method for indication of increased risk of a person for developing Parkinson's disease, but may not identify all individuals who may be at risk for developing the disease.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high as shown by the cited prior art, and the specification provides one with little description or guidance that leads one to increasing the sensitivity of the method of diagnosis, especially since the frequency of ADH1C stop mutations in patients with Parkinson's disease is relatively low. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further, the specification does not provide guidance to overcome art recognized problems in diagnosis required to actually use the diagnostic methods as broadly claimed. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the small number of working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written.

Allowable Subject Matter

4. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim. No prior art was found that teaches a method for identifying a person at increased risk for developing Parkinson's disease, comprising screening nucleic acids from said person for a mutation in an ADH1C gene which encodes a truncated form of

the expressed protein chain, wherein the mutation corresponds to a thymidine at or corresponding to position 303 of SEQ ID NO. 1 within a cDNA or other sequence of ADH1C.

Response to Arguments

5. Applicant's arguments filed November 29, 2006 have been fully considered but they are not persuasive.

The amendment to claim 1 overcomes the 35 U.S.C. 112, first paragraph scope of enablement rejection since the invention as now claimed is designed to identify a person at increased risk for developing Parkinson's disease. However, claims 1 and 3-6 are rejected under 35 U.S.C. 112, first paragraph since these claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. In particular, a limitation of the claims is screening nucleic acids from a person for a mutation in an ADH1C gene which causes a truncation of the expressed protein chain. However, the specification describes only one such truncation, the G303T (G78) stop mutation. There is not mention of other mutations that may lead to a truncation of the expressed protein chain or any statements or evidence that rule out the possibility that no other truncation mutations other than the G78 mutation can occur or are phenotypically detectable. Therefore, the claims are not fully enabled since there is no teaching in the specification to enable one skilled in the art to detect any truncation mutation in an ADH1C gene that may be associated with a person having increased risk for developing Parkinson's disease.

Claim 2 is objected to as being dependent upon a rejected base claim, but in view of the present amendment to the base claim, would be allowable if rewritten in independent form including all of the limitations of the base claim. No prior art was found that teaches a method for identifying a person at increased risk for developing Parkinson's disease, comprising screening nucleic acids from said person for a specific mutation in an ADH1C gene which encodes a truncated form of the expressed protein chain, wherein the mutation corresponds to a thymidine at or corresponding to position 303 of SEQ ID NO. 1 within a cDNA or other sequence of ADH1C.

Conclusion

6. Claim 1 and 3-6 are rejected. Claim 2 would be allowable if rewritten in independent form including all of the limitations of the base claim as discussed above.

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER